# Four-Year Review of Sildenafil Citrate

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*Within 6 months of approval by the U.S. Food and Drug Administration (FDA), 5.3 million prescriptions were written for sildenafil citrate. It represented the first clearly effective and FDA-approved oral therapy for the treatment of ED. The chemical structure of sildenafil is very similar to the cyclic guanosine monophosphate molecule with which it competes, in the enzyme phosphodiesterase type-5. Sildenafil binds to the phosphodiesterase-5 enzyme, preventing the breakdown of cyclic guanosine monophosphate through competitive inhibition. The onset of action for sildenafil can be as short as 20 minutes and the duration of action may be as long as three half-lives (18 hours). Anecdotal evidence suggests that many men describe an erectogenic effect for almost 24 hours. The safety of sildenafil has been established in many pre- and post-approval studies at doses as high as eight times the maximum recommended dose. It is likely that the rare instance of myocardial infarction after taking sildenafil as directed, is due more to the activity of sexual intercourse rather than the medication itself. Efficacy have been established in patients with diabetes, parkinsonism, spinal cord injury, and those on antihypertensive (single- and multiple-therapy) agents. It has also been shown to be effective in reversing selective serotonin reuptake inhibitor–induced sexual side effects. Initial concerns about sildenafil with respect to ocular safety were based on misinterpretation of the FDA submission data. The two most common side effects are headache and flushing, both of which are short-lived and easily treated.* [Rev Urol. *2002;4(suppl 3):S26–S38*]



**Key words**: Sildenafil • Nitric oxide • Phosphodiesterase-5 inhibitor • Cyclic guanosine monophosphate • Diabetes • Hypertension • Cardiovascular disease

There is no doubt that the discovery and development of sildenafil has been a revolutionary event in medicine and society. The discovery was paved by the Nobel prizewinning efforts of Drs. Furchgott, Ignarro, and Murad, who discovered the link between nitric oxide (NO) and the human cardiovascular system. NO is the neurotransmitter that signals the nutrient blood vessels of the heart to relax and increase their flow. Researchers took this concept one step further and focused on the synthesis of a phosphodiesterase-5 inhibitor (PDE-5) that would

**Table 1**
**Phosphodiesterase Family Tree**
**(11 Families, 21 Subfamilies, 53 Isoforms)**

| | Phosphodiesterase Family | Subfamily | Splice Variants |
|---|---|---|---|
| All discovered pre-sildenafil | 1 | A | 4 |
| | 1 | B | 1 |
| | 1 | C | 5 |
| | 2 | A | 3 |
| | 3 | A | 1 |
| | 3 | B | 1 |
| | 4 | A | 8 |
| | 4 | B | 3 |
| | 4 | C | 4 |
| | 4 | D | 5 |
| | 5 | A | 3 |
| | 6 | A | 1 |
| | 6 | B | 1 |
| | 6 | C | 1 |
| All discovered post-sildenafil | 7 | A | 3 |
| | 7 | B | 1 |
| | 8 | A | 1 |
| | 8 | B | 1 |
| | 9 | A | 4 |
| | 10 | A | 2 |
| | 11 | A | 4 |

potentiate the effects of NO in the cardiovascular system. The molecule UK-92-480, later known as sildenafil, was synthesized and brought forth for clinical trials in 1991 after promising animal studies showed that sildenafil induced coronary artery dilatation.

Early human trials in 1991 and 1992 established that sildenafil was not promising as an antianginal drug; however, as an "adverse event" in the trials, men were reporting an erectogenic effect from the medication. In 1992, at the University of California, Los Angeles, the link between NO and erections was established. Dr. Jacob Rajfer and his collaborators clearly showed the link between NO and penile smooth muscle relaxation during penile erection.[1-3] In late 1993, the first study of sildenafil for the treatment of erectile dysfunction (ED) was so successful that men and their partners protested when the trials were completed and the medication withdrawn; open-label extensions were added to the placebo-controlled studies. The addition of open-label trials enabled the manufacturer not only to provide "humanitarian relief" to couples who had been given a temporary reprieve in their battle with ED, but also to collect valuable long-term open-label safety and efficacy data. By the time the manufacturer was ready to submit to the U.S. Food and Drug Administration (FDA) on September 29, 1997, over 4500 men had been tested—far more than the average number tested in the course of a typical drug development. Because this medication "fulfilled a significant medical need or represented a significant medical advance in therapy," the FDA notified the manufacturer that it would give sildenafil citrate a priority review. Approval was anticipated within 6 months instead of the usual 12 months.

The approval of sildenafil brought on a worldwide maelstrom of publicity, unprecedented in the medical or pharmaceutical industry. With a potential pool of 20–30 million men at risk for ED, financial experts were anticipating sales of up to $4 billion per year internationally. Prior to the approval, less than 4% of men sought medical attention for ED, and the available treatments were limited and invasive. A deluge of men seeking treatment therapy was expected and did indeed occur. Within 6 months, 5.3 million prescriptions were written; within 2 years, 20% (6 million) of men at risk for ED had been treated with sildenafil citrate, and the drug swiftly captured 98% of the market for the treatment of ED.

*As an "adverse event" in the trials, men were reporting an erectogenic effect from the medication.*

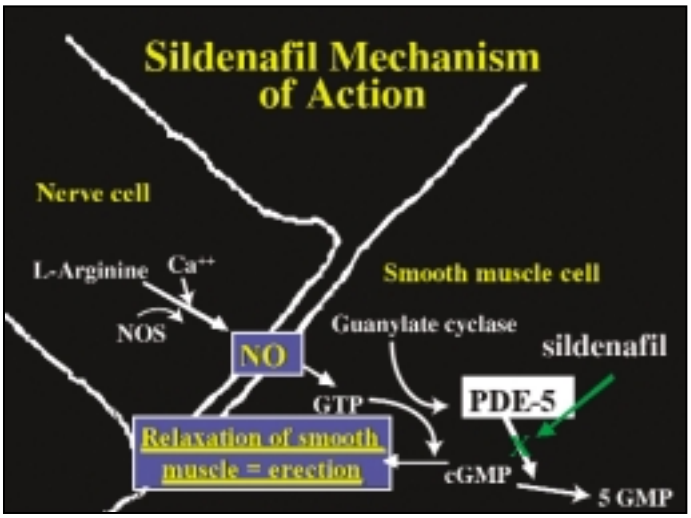


Figure 1. *Sildenafil mechanism of action.*

## How Does It Work?

Sildenafil works as a competitive inhibitor of an enzyme of the phosphodiesterase type five class (PDE-5). There are eleven types of phosphodiesterase found throughout the body; almost half of them were discovered after 1997 (Table 1). PDE-5 is found in the corpus cavernosum, platelets, skeletal muscle, and vascular and visceral muscle. Although types 2, 3, 4, and 5 are all found in the penis, type 5 is the predominant isoform in the penis.[4,5]

When stimulation occurs in the nonadrenergic and noncholinergic nerves in the pelvic parasympathetic plexus through sexual or physical stimulation or erotic fantasies, the neurotransmitter NO is released across the neuromuscular junctions of the penile arteries and cavernosal smooth muscles. NO then causes an increase in the molecule cyclic guanosine monophosphate (cGMP), which in turn results in relaxation of the penile smooth muscle, creating an increased penile blood flow, cavernosal smooth muscle relaxation, and finally penile tumescence and rigidity. PDE-5 breaks down the cGMP, resulting in a contraction of the penile arteries and smooth muscle and causing detumescence (Figure 1). Anything that will potentiate the cGMP by preventing its breakdown (in effect increasing its local concentration) or by increasing its production will have a salutatory effect on erectile function.

The chemical structure of sildenafil is very similar to cGMP (Figure 2). Sildenafil binds to the PDE-5 enzyme, preventing the PDE-5 breakdown of cGMP through competitive inhibition. Many of the risk factors associated with ED—age, hypertension, diabetes, and dyslipidemia—have been shown to be associated with decreased endothelial levels of nitric oxide synthase (NOS), the enzyme that produces NO. Diminished NO synthesis results in decreased NO and, secondarily, less available cGMP for smooth muscle relaxation. It is small wonder that sildenafil is effective across all etiologies. Nonetheless, if the ED is due to neuronal loss, as is the case after non–nerve-sparing radical prostatectomy, or if there is severe arterial disease where the fixed vasculopathy prevents any degree of arterial smooth muscle relaxation, sildenafil is unlikely to be effective.

Sildenafil is absorbed rapidly in the small intestine after oral administration, with times to peak plasma concentration from 30 to 120 minutes.[4] Anything that delays gastric emptying will delay the time to peak plasma concentration. A high-fat meal will cause such a delay in gastric emptying and can delay the time to peak plasma concentration by 60 minutes and reduce the peak plasma concentration by 29%. Peak efficacy is seen after taking the medication on an empty stomach, where clinical efficacy has been observed within 19 minutes.[4]

Figure 2. *Sildenafil is a competitive inhibitor which resembles cyclic guanosine monophosphate (the substrate) and binds to the active site of phosphodiesterase-5.*

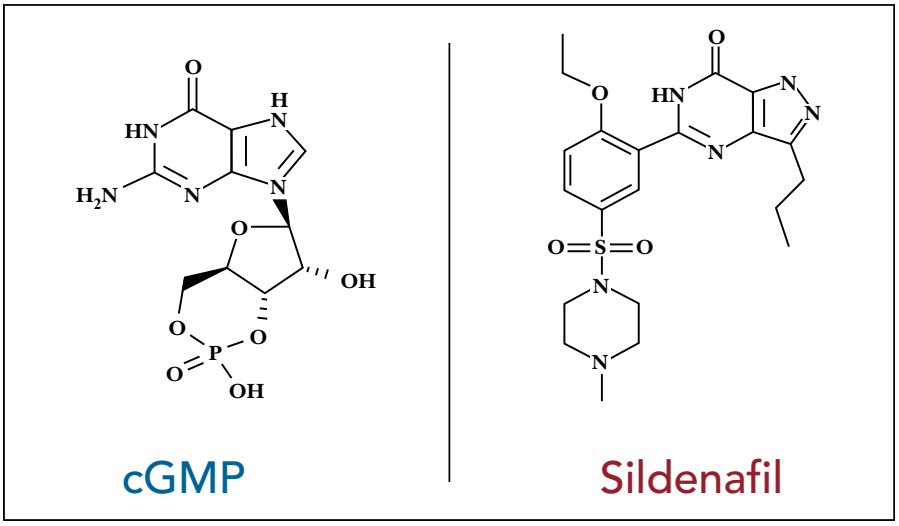

**Table 2**
**Exclusion Criteria for Sildenafil Trials**

| |
|---|
| Genital abnormalities |
| History of alcoholism or substance abuse |
| MI, stroke, or unstable angina within the last 6 months |
| Uncontrolled hypertension or hypotension |
| Nitrates |

Tumescence as assessed by RigiScan activity (Timm Medical Technologies, Eden Prairie, MN) has been observed at 12 minutes, with 80% of men showing activity by 30 minutes. Activity at 24 hours has not been assessed.

Sildenafil is metabolized by the cytochrome p-450, 3A4, and 2C9. Any inhibitor of these enzymes (cimetidine, erythromycin, and ketoconazole) may result in delayed metabolism and may require a dose adjustment. Nonetheless, in the clinical trials men on these cytochrome p-450 inhibitors did not experience an increase in adverse events over the other study patients, despite a lack of dose adjustments. Though increased serum concentrations may be associated with more adverse events, the safety of sildenafil has been established in doses eight times the maximum recommended dose of 100 mg. In the presence of the protease inhibitor ritonavir, which shares both metabolic pathways with sildenafil, sildenafil should not be co-administered at a dose greater than 25 mg over a 48-hour period. The major metabolite of sildenafil is approximately 50% as potent as its parent compound with a comparable terminal half-life. The duration of action for sildenafil may be as long as three half-lives, and anecdotal evidence suggests that many men will describe an erectogenic effect for almost 24 hours.

## How Well Does It Work and What are the Side Effects ?

Initially there was skepticism as to how an oral pill could work selectively on the penis. The pivotal trials had been purposely designed to reflect a typical practice experience with liberal inclusion criteria (Table 2). Patients had to have physician documentation of ED for 6 months and be in a steady heterosexual relationship. The heterosexual requirement was necessary because all of the questionnaires used to measure efficacy had been validated with heterosexual couples using vaginal penetration as an endpoint. There were limited restrictions as to etiology, be they physical, psychological, or both.

Though this medication compiled an impressive "track record" on paper, the efficacy endpoints, which included validated questionnaires, were difficult to translate into real-world experience. Though there has been a tremendous improvement in the methods to evaluate efficacy with the introduction of several statistically validated multilingual questionnaires (Table 3), it remains difficult to compare efficacy endpoints between publications because of the lack of standardization of reporting methods. With the advent of new therapies, the comparison of drugs without direct comparator trials will be meaningless.

The overall improvement in erection with treatment in the pivotal American 12-week, placebo-controlled study evaluated by a global efficacy question (GEQ) was 74% versus 16% with placebo. What would that mean to the millions of men who would be taking sildenafil? It did not take long to find out, as millions of men flocked to pharmacies throughout the country seeking sildenafil. Physicians and patients reported over 70% success rates.[6–11] The experience in the clinical trials was reflected positively in real-world experience.

Other than two early inpatient trials on diabetics and spinal cord injury patients, no attempt had been made to focus on the efficacy in one particular risk-factor group. Subsequently multiple studies and analyses have been carried out for all the risk-factor groups with ED (Table 4).

## Age

Age is an independent risk factor for ED from which no males can escape. The relationship between age as an independent risk factor and ED has been well established throughout the medical literature.[12–15] Among men over 40, 52% will have ED, the severity of which increases with age. As the population is aging and the aged population is healthier, quality-of-life issues such as ED will need to be addressed. Wagner and colleagues reviewed five double-blind, placebo-controlled studies of the efficacy and tolerability of sildenafil in 482 elderly men (65 years or older). Efficacy was assessed using a GEQ, questions 3 and 4 of the International Index of Erectile Function (IIEF), and the five sexual function domains of the IIEF. All efficacy assessments indicated that sildenafil significantly improved erectile function both in elderly patients with ED of broad-spectrum etiology and in elderly patients with

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**Table 3**
**Methods of Measuring Efficacy of Treatment for Erectile Dysfunction**

| Evaluation Method | Acronym |
|---|---|
| International Index of Erectile Function (By domains or global) | IIEF |
| O'Leary Brief Male Sexual Function Inventory | BMSFI |
| Sexual Health Inventory for Men | SHIM |
| Arizona Sexual Experience Scale | ASEX |
| Global Efficacy Question | GEQ |
| Sexual Encounter Profile | SEP |
| Patient Event Log | |
| Partner Event Log | |
| Nocturnal Penile Tumescence | NPT |
| Penile Tumescence with Visual Sexual Stimulation | VSS |

ED and diabetes. The most common adverse events were mild-to-moderate headache, flushing, and dyspepsia; rates of discontinuation due to adverse events were low and were comparable to the rates with placebo.[16]

## Diabetes

Diabetes represents a major risk factor for ED.[17–19] Among men with ED, 15% will be diabetic, and 50% of diabetics will develop some degree of ED after 5 years of disease. The underlying cause may be poor glycemic control, progressive diabetic vasculopathy, neuropathy, and myopathy, as well as underlying depression. Preapproval inpatient studies demonstrated a 52% sildenafil response rate by patient questionnaires and nocturnal penile tumescence studies.[20] The sildenafil response rate among diabetics in the pivotal trials was one of the lowest of all the organic etiologies. Subsequent to its approval there have been many studies specifically looking at diabetic men. Rendell and colleagues,[21] in a placebo-controlled, multinational study of 268 men, demonstrated a successful intercourse rate of 56% with sildenafil versus 22% with placebo. In a recent study looking at type II diabetics, Boulton and colleagues found that sildenafil was effective in type II diabetics with more than one diabetic complication and with poor glycemic control.[22]

## Hypertension

Among men with ED, 20%–39% will have a risk factor of hypertension,[23] and over 20% of hypertensive men have ED.[24] Though hypertension may cause ED through hypertensive vasculopathy, cardiovascular disease, and endothelial disease, many men will describe the onset of their ED with initiation of antihypertensive therapy.[12] Whether it is the medication or the desired lowering of the blood pressure that causes the ED is not well understood. It is clear, however, that changing the antihypertensive medication rarely restores erectile function.[25] For that reason, it is imperative to have a medication that effectively counteracts this common side effect of successful antihypertensive therapy. To have such an "antidote" to combat antihypertensive medication–induced ED can only help in compliance with a drug regimen that has intangible beneficial results.

A substantial number of patients and a minority of physicians may question the safety of using sildenafil in patients with medicated hypertension. Kloner[26] reviewed the efficacy of sildenafil in 3414 men, 1218 of whom were taking antihypertensive medication; patients received sildenafil or placebo in 10 double-blind studies. The improvements in erectile function and adverse events (hypotension, dizziness, and syncope) demonstrated in sildenafil-treated patients were comparable in patients taking and those not taking antihypertensive medication.

Safety was assessed in 3975 men, 1094 of whom were taking one or more antihypertensive agent, classified as a diuretic, β-blocker, $\alpha_1$-blocker, angiotensin-converting enzyme inhibitor, or calcium channel blocker; they received sildenafil or placebo in 18 double-blind, placebo-controlled studies. The number and type of antihypertensive medications from among the five classes had no effect on the adverse-event profile of sildenafil.[26] There was no increased risk of myocardial infarction, stroke, or death between the sildenafil and the placebo group. In a study by Zusman, no clinically significant differences were found in systolic blood pressure, diastolic blood pressure, and heart rate between the patients taking and those not taking antihypertensive medication.[27]

## Cardiovascular Disease

Men with cardiovascular disease (CVD) are more likely to have ED than the general population, because both conditions share risk factors

**Table 4**
**Risk Factors for Erectile Dysfunction**

| Medical | Nonmedical |
|---|---|
| Age[83,84] | Occupation (blue vs white collar)[85] |
| Cardiovascular disease[84,86] | Education (low vs high)[85] |
| Hypertension[24,84,87,88] | Marital or relationship difficulties |
| Diabetes[17,18,84,88–90] | Level of physical activity |
| Dylipidemia[84,91,92] | Anxiety |
| Neurological (stroke, multiple sclerosis, spinal cord injury, Parkinson's disease, spina bifida)[37,38,93,94] | Stress[85] |
| Surgery (vascular, colorectal, prostate)[95–97] | Personality types[98] |
| Prostate cancer & treatment (external beam, interstitial seeds, or radical surgery)[57,60,99–103] | |
| Renal failure[104] | |
| Depression[105] | |
| Medication[24,106] | |
| Smoking[107–109] | |
| Obesity[109,110] | |
| Nonprostate cancer and radiation therapy or chemotherapy[111–113] | |
| Hormonal[70,114] | |

and some drugs used to treat CVD may induce ED as a side effect. Three months after its approval, reports began to trickle into the FDA about sildenafil-related deaths, though they were not directly attributable to sildenafil. In June of 1998 the FDA, in response to public pressure, set up an unprecedented website that reported all sildenafil-related deaths, whether they were causal or not. In fact, none were ever directly attributable to sildenafil. Men with a history of CVD, a major comorbidity of ED, presented a dilemma for physicians and patients. Could this "lifestyle drug" be dangerous? Did the FDA push the drug through the regulatory process too fast?

In the clinical trial database, the incidence of any cardiovascular adverse events was 3% in the sildenafil group and 3.5% in the placebo group. The rate of medication discontinuation due to cardiovascular events was 0.9% and similar in the sildenafil and placebo groups.[28]

Muller and colleagues, in a study prior to the approval of sildenafil, had shown that the relative risk of myocardial infarction (MI) occurring in the 2 hours following sexual activity was 2.5. In men with a prior history of MI, that risk increased to 2.9. The risk of an MI, though real, was small. Only 0.9% of MIs were considered to have been triggered by sexual activity.[29] In a comprehensive review of 53 sildenafil trials with 6884 patient-years of exposure to sildenafil and 543 patient-years of exposures to placebo, the MI and death rate per 100 patient-years were 1.11 and 0.74 and 0.8 and 0.42 in placebo and sildenafil, respectively.[30] Though it might be thought that sildenafil would have a beneficial effect on MI and death rates during sexual intercourse because of its vasodilatory effect on the coronary arteries, the differences between the sildenafil and placebo groups were not statistically significant. It is certainly likely that MI after taking sildenafil as directed is more likely to be due to the activity of sexual intercourse rather than the medication itself.

Further evidence for the safety of sildenafil in men with ischemic heart disease was demonstrated by Herrmann and colleagues.[31] Many cardiologists were concerned that in men with ischemic disease of the coronary arteries, administration of sildenafil would result in a "steal syndrome" by dilating nondiseased arteries. The diverted blood flow would then result in exacerbation of ischemic disease during the physical exertion of sexual intercourse. Herrmann assessed the systemic, pulmonary, and coronary hemodynamic effects of oral sildenafil (100 mg) in 14 men with severe stenosis of at least one coronary artery (stenosis of >70 percent of the vessel diameter) who were scheduled to undergo percutaneous coronary revascularization. Coronary blood-flow velocity and flow reserve were assessed with a Doppler guidewire in 25 coronary arteries, including 13 severely diseased arteries and 12 arteries without stenosis as a reference. Oral sildenafil produced only small decreases (<10%) in systemic arterial and pulmonary arterial pressures, and it had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, or cardiac output. There were no significant changes in average peak coronary

flow velocity, coronary-artery diameter, volumetric coronary blood flow, or coronary vascular resistance. As one might expect, coronary flow reserve at baseline was lower in the stenosed arteries than in the reference arteries and increased significantly in both groups of arteries combined after the administration of sildenafil. The ratio of coronary flow reserve in coronary arteries with stenosis to that in the reference arteries was not affected by sildenafil. It was concluded that no adverse cardiovascular effects of oral sildenafil were detected in men with severe coronary artery disease and that a small positive effect on coronary blood flow reserve was seen. Perhaps the beneficial effect of sildenafil on the heart circulation that was originally observed in animals in 1991 (Pfizer, data on file) also occurs during sexual intercourse in men with ischemic heart disease.[32]

In 1999, the Princeton consensus panel was convened to develop recommendations for clinical management of sexual dysfunction in patients with cardiovascular disease. Based upon a review of the research and presentations by invited experts, a classification system was developed for stratification of patients into high, low, and intermediate categories of cardiac risk. A simple algorithm was provided for guiding physicians in the management of sexual dysfunction in patients with varying degrees of cardiac risk.[33]

Postlaunch efficacy studies have shown efficacy rates of over 70% in men with CVD. Side-effect profiles were comparable to other groups with organic ED.[34]

## Neurologic Disorders

Patients with upper and lower motor neuron lesions invariably suffer from ED. Men with upper motor neuron lesions (stroke, spinal injury, multiple sclerosis, parkinsonism) will have attenuation of the signal from the central nervous system, resulting in difficulty achieving and sustaining their erectile function. With sildenafil, the neurological signal is amplified and sustained, resulting in better erectile function. Hussain and colleagues looked at the efficacy and safety of sildenafil in men with parkinsonism (n = 12) and multisystem atrophy (n = 6). The sildenafil was effective in men with parkinsonism, as demonstrated by IIEF questionnaire responses, with minimal changes in blood pressure between active and placebo medication. In multiple-system atrophy, six patients were studied before recruitment was stopped because three men showed a severe drop in blood pressure 1 hour after taking the active medication. Two of these men were already known to have orthostatic hypotension and were receiving treatment with ephedrine and midodrine, but the third had asymptomatic hypotension. Despite a significant postural fall in blood pressure after sildenafil, all patients with multiple-system atrophy reported a good erectile response and were reluctant to discontinue the medication.[35] Zesiewicz and colleagues reported similar beneficial results in 10 men with parkinsonism. Improvement was seen in all domains of the sexual health inventory for men.[36]

*Men with spinal cord injury are usually younger than men typically seeking treatment for ED and are concerned about their sexual dysfunction, which is virtually universal in this subpopulation.*

Multiple sclerosis (MS) is a progressively disabling disease associated with deterioration in sexual dysfunction is as many as 82% of men and 52% of women.[37,38] Green and colleagues investigated the use of sildenafil in 7 patients with MS and demonstrated a response rate and side-effect profile comparable to other trials in neurologically impaired patients.[39]

Men with spinal cord injury (SCI) are usually younger than men typically seeking treatment for ED and are concerned about their sexual dysfunction, which is virtually universal in this subpopulation. Neurological rehabilitation centers frequently concentrate on the return of motor function and seldom address sexual rehabilitation. This oversight is particularly worrisome considering the dramatic response rates to sildenafil in these individuals who have recently undergone an event that drastically worsens their quality of life. Quality-of-life improvement after sildenafil treatment was examined in an international study of 178 men with SCI. Improvements were reported in scores for the generic quality-of-life parameters of mental health, well-being, depression, and anxiety ($P < 0.05$ sildenafil vs placebo).[40] In a study of 41 men with varying degrees of SCI, Schmid reported a sildenafil response rate of 93%. The most common dose required to achieve a satisfying erection was 50 mg. The side-effect profile was comparable to other studies. Sildenafil efficacy was dependent on sparing of either sacral (S2-S4) or thoracolumbar (T10-L2) spinal segments. Complete disturbance of any neurogenic impulses precluded successful treatment.[41] A beneficial effect of sildenafil was also seen in sexual arousal in women with spinal cord injury.[42]

## Depression

Erectile dysfunction has been independently associated with depression.[43] In addition to its independent

association, the medications used to treat depression themselves induce sexual dysfunction, in the form of decreased libido, erectile dysfunction, and orgasmic dysfunction, in as many as 59% of patients.[44,45] The sexual dysfunction associated with the medication for depression can be a significant reason for therapeutic noncompliance on the part of patients. Several postapproval studies address the treatment of ED associated both with depression and with treatments for depression.

Fava and colleagues demonstrated in an open-label trial the benefit of sildenafil in reversing selective serotonin reuptake inhibitor (SSRI)–induced sexual side effects. In 14 subjects (9 men and 5 women), statistically significant improvements were see in all domains of sexual functioning, including libido, arousal, orgasm, sexual satisfaction, and (in males only) erectile function, and 69% of patients reported much or very much improved function.[46] In a retrospective analysis of 10 placebo-controlled fixed- and flexible-dose trials in 98 male patients (65 on sildenafil and 35 on placebo), patients with erectile dysfunction receiving serotonergic antidepressants had significantly greater improvements in ability to achieve and maintain an erection, frequency of ejaculation, and orgasm frequency on sildenafil than on placebo.[47] It is apparent that men on SSRIs should be aggressively screened for sexual dysfunction, as SSRI-induced sexual dysfunction can easily be treated with sildenafil.

It is difficult to determine how much depression contributes to ED and how much ED contributes to depression. In a study of 152 men with untreated mild depression and ED, successful treatment of the ED resulted in a 50% decrease in Hamilton depression scale scores. Improvement of erectile dysfunction was associated with marked improvement in depressive symptoms and quality of life.[48] This was a select group of men, and the results should not be interpreted to show that all men with depression should be treated with sildenafil. The trial only underscores the importance of screening for ED in men with depression.

## Prostate Cancer Patients

Though men with prostate cancer represent a small percentage of men with ED, virtually all the men are negatively affected sexually by the disease or its treatment. The age group generally affected by prostate cancer is usually the sixth decade of life, when the incidence of erectile dysfunction is already well over 50%. The etiology of erectile dysfunction in the prostate cancer patient varies.

Immediately after the diagnosis of prostate cancer, many men will experience a reactive depression with a loss of libido, which can lead to decrease in erectile function.[49] This period of sexual dysfunction varies according to underlying coping mechanisms, and a majority of men are able to recover.

After radical prostate surgery, all men will experience at least temporary erectile dysfunction due to neuropraxia, nerve denervation, and/or secondary corporal muscle myopathy.[40,51] The nerve injury after radical retropubic prostatectomy (RRP) is a lower motor neuron injury; NO is not produced in sufficient quantities because of the denervation. Because intact neuromuscular connections are required for sildenafil to work, men must have a subtotal nerve injury in order for sildenafil to be effective. One would not expect men who have undergone bilateral nerve resection to respond to sildenafil, though a 10% potency rate was usually quoted prior to description of the nerve-sparing prostatectomy. Zippe examined the efficacy of sildenafil in 91 men seeking treatment for ED after radical prostatectomy.[52,53] He found that after bilateral nerve-sparing prostatectomy (BNS), 71.7% (38 of 53) responded to sildenafil; after unilateral nerve sparing (UNS), 50% (6 of 12) responded; and after non-nerve-sparing (NNS), 15.4% (4 of 26). The sildenafil response rates are better than in the original pivotal trials (42%), which were not stratified according to nerve-sparing status. The side effects were those typically seen in all the sildenafil trials: transient headaches (28.6%), flushing (21.9%), dizziness (8.8%), dyspepsia (6.5%), and nasal congestion (5.4%). Age was found to be a significant predictor of response rate in men after BNS[54]; in a study examining 327 patients at least 18 months after RRP, the sildenafil satisfaction rates by Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire were 80%, 66%, and 32% in men under 55, between 55 and 65, and over 65, respectively.[54]

Like RRP, the effect of pelvic and prostatic radiation on potency is age-dependent. Unlike RRP, in which erectile function improves with time, erectile function after radiation therapy (RT) worsens over time[55] as the radiation takes its toll on the microvascular, neurologic, and smooth muscle components of the penis and the prostate.[56] Though men will describe a de novo low ED rate within the first 12 months after RT,[57,58] ED rates at 5 years approach 65%.[59,60] Regardless of the etiology and the actual potency rates, the successful response rate to sildenafil is between 70% and 80%.[55,57,59,61–63]

Notably missing in the literature is the effect of sildenafil on androgen deprivation–induced erectile dysfunction.

## Renal Failure and Dialysis

A late manifestation of aging, hyper-

tension, peripheral vascular disease, and diabetes is renal failure. Many of these men experienced decreased libido from their chronic disease, and one would expect that in men with such devastating complications, sildenafil would have lowered efficacy. The incidence of erectile dysfunction in hemodialysis and continuous ambulatory peritoneal dialysis (CAPD) can reach 80%,[64,65] with approximately 60% recovering function after transplantation.[66,67]

In a CAPD unit all patients were evaluated for ED. Of these, 32 men were considered to have ED, and 15 patients agreed to be in the trial. Only 6 completed the 12-week trial, with only 2 reporting a satisfactory response.[68] Another small study of 35 men reported an 80% success rate (28/35), but 3 patients dropped out because of intolerable headaches, yielding a long-term efficacy rate of 71%. In a largely black cohort of patients with renal failure, a 66% satisfaction was reported.[69]

In a posttransplant study of 50 men, 60% reported a satisfactory response, with no patients discontinuing therapy because of side effects. The response rate seem to be inversely correlated with the time spent on dialysis.[66]

## Hormones

Hormonal replacement was the mainstay of medical treatment prior to the advent of intracorporal injection therapy and sildenafil. There is a gradual decline in testosterone with age, but few men (<6%) reach true hypogonadism and less than 12% of men with ED are hypogonadal.[70] The replacement of androgens in men with "low normal" levels and ED has never been shown to restore normal function. It is far preferable to treat the ED (4–6 times a month) with medication that is selective for the end organ, than altering the hormonal milieu and creating a treatment that requires daily topical to monthly injectable replacement. There are no studies on the treatment of truly hypogonadal men with sildenafil.

## Other Issues and Future Directions

### *Tachyphylaxis*

Long-term data do not support the concept that men will not respond to sildenafil in time. Long-term data are available on 245 men where 95% of men reported maintained efficacy. In time, we will see men reporting decreased efficacy as their underlying disease process, whatever it might be, progresses. As the diabetic vasculopathy, neuropathy, and myopathy progress, so too will the severity of the ED. A study by El-Galley suggested that tachyphylaxis might exist with sildenafil. Poor follow-up of the study cohort (54%), a low sample size, and poor methodology preclude any such statements.[71] Though tachyphylaxis may theoretically exist, the El-Galley study did

### Main Points

- Sildenafil is a competitive inhibitor of an enzyme of the phosphodiesterase type five class (PDE-5).
- Eleven types of PDE are found throughout the body; PDE-5 is found in the corpus cavernosum, platelets, skeletal muscle, and vascular and visceral muscle and is the predominant isoform in the penis.
- Stimulation of the nonadrenergic and noncholinergic nerves in the pelvic parasympathetic plexus leads to release of nitric oxide (NO) across the neuromuscular junctions of the penile arteries and cavernosal smooth muscles.
- NO causes an increase in the molecule cyclic guanosine monophosphate (cGMP), which in turn results in relaxation of the penile smooth muscle, creating an increased penile blood flow, cavernosal smooth muscle relaxation, and finally penile tumescence and rigidity.
- PDE-5 breaks down the cGMP, resulting in a contraction of the penile arteries and smooth muscle, and causing detumescence.
- If erectile dysfunction is due to neuronal loss, as is the case after non–nerve-sparing radical prostatectomy, or if there is severe arterial disease where the fixed vasculopathy prevents any degree of arterial smooth muscle relaxation, sildenafil is unlikely to be effective.
- Sildenafil is absorbed rapidly in the small intestine after oral administration, with times to peak plasma concentration from 30 to 120 minutes; peak efficacy is seen after taking the medication on an empty stomach, where clinical efficacy has been observed within 19 minutes.
- Sildenafil significantly improved erectile function both in elderly patients with ED of broad-spectrum etiology and in elderly patients with ED and diabetes.
- Sildenafil was found to be effective in type II diabetics with more than one diabetic complication and with poor glycemic control.
- Dramatic response rates have been found in men with spinal cord injury.

not provide any convincing evidence. Pharmacologically it is unlikely that a medication that is used 4 to 6 times a month would result in up- or down-regulation of the PDE-5 enzymatic reaction.

*Visual Safety*

One of the first safety concerns about sildenafil was with respect to ocular safety. The concerns were based on misinterpretation of the FDA submission data.[72,73] Sildenafil is weakly reactive to PDE-6, which plays a role in phototransduction. It is 10-fold more selective to PDE-5 than PDE-6. Exhaustive animal safety studies at prolonged (2 years) pharmacologic doses revealed no functional or morphological alterations in the retina or optic pathway (Pfizer, data on file). Human studies have included noninvasive visual function tests such as visual acuity, visual fields, contrast sensitivity, intraocular pressure, Amsler grid, and recovery from photostress, as well as color discrimination tests.[74] The color discrimination test was the only one that showed transient disturbance manifested by temporary difficulty in discriminating blue-green hues. The effect is transient and dose-related, with an overall incidence of 3% at the maximum dose of 100 mg. Luu and colleagues examined the effect of sildenafil on the electroretinogram and found that within 5 hours of a 200 mg dose, the cone function was slightly depressed in the macula and periphery. However, the affected electroretinogram and multifocal electroretinogram parameters still remained within normal limits.[75] With millions of men having taken the drug, no subtle ophthalmologic concerns have arisen.

*Overall Side Effects*

Throughout all the studies performed so far, the side effects have been found to be a direct consequence of PDE-5 inhibition, vasodilatation, and gastroesophageal (GE) sphincter relaxation. Though the side effects may vary slightly from one study to the next, the nature is constant and they appear to be dose-related. The two most common side effects are headache (16%) and flushing (10%), both of which are short-lived and easily treated. Though seemingly innocuous to the physician, an uninformed patient may nonetheless interpret the side effect as dangerous and may unnecessarily and prematurely discontinue the medication.

Dyspepsia occurs in approximately 7%. The cause of the dyspepsia is an esophagitis that occurs with the PDE-5 inhibition–induced relaxation of the GE sphincter and GE reflux. This side effect can be troublesome to the patient because it occurs several hours after taking the medication. The patient may not associate the "heartburn" with having taken sildenafil and may associate it with angina, particularly if he has any cardiac history. Again, simple instruction on the part of the physician or his extender may alleviate unnecessary fear and anxiety on the part of the patient.

## Future Directions

*Female Sexual Dysfunction*

The use of sildenafil in female sexual dysfunction (FSD) is controversial. FSD is not as easily measured as ED. Many of the objective tests do not correlate with perceptions of the patients. Nonetheless, sildenafil has been shown to be effective in reversing the sexual dysfunction side effects of SSRIs in females,[76–78] sexual arousal disorders,[79,80] and spinal cord injury–induced sexual dysfunction.[42] Large-scale trials are needed better to define the role of sildenafil in FSD.

*Pulmonary Hypertension*

Primary pulmonary hypertension (PPH) is a rare disease of childhood that carries a poor prognosis. Pharmacological intervention is directed towards reduction of the raised pulmonary artery pressure with vasodilator treatment. PDE-5 hydrolyzes cGMP in the lung, thereby modulating NO-mediated pulmonary vasodilation. Inhibitors of PDE-5, such as sildenafil, have been proposed for the treatment of PPH. In addition to case reports,[81] in a small study with 5 patients, sildenafil caused a long-lasting reduction in mean pulmonary artery pressure and pulmonary vascular resistance, with a further additional improvement after iloprost inhalation. These data suggest that small doses of a phosphodiesterase type 5 inhibitor may be a useful adjunct to inhaled iloprost in the management of PPH.[82] Further off-label investigations in the use of sildenafil in PPH are ongoing.

## Summary

Sildenafil:

- Has revolutionized the treatment of erectile dysfunction.
- Has improved the quality of life of millions of men and their partners.
- Continues to find niches in treating disease conditions.
- Exemplifies a near-perfect blend of basic science, academic medicine, and the pharmaceutical industry. ■

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### Summary of Discussion Following Dr. McCullough's Presentation

Dr. McCullough stressed two important points made during his presentation:

1. The safety and efficacy track record of sildenafil for the past 4 1/2 years is very good. The original clinical trial data has been validated by the post launch data, in millions of men.
2. When comparing studies we need to carefully look at two things: First, what are the entry criteria for the study? What was the degree of ED at the starting point? Second, what endpoints were used to establish efficacy?

Dr. Sadovsky raised the point that sildenafil is unique compared to other non–ED medications, in that how it is taken and the instructions given are so important to its efficacy. He suggested that time be spent on the topic, "What is the minimum amount of advice and counseling that should be given to a patient?"

The issue of spontaneity was brought up. Dr. McCullough observed that when he sees patients who complain about the lack of spontaneity with a medication that has to be taken one hour before sexual intercourse, he asks them, "When do you normally have sex, in the morning or evening?" At age 55, one's life usually is routinized, and as "creatures of habit" we know if we are going to be sexually active in the morning, midday, or evening. Furthermore, most patients can usually predict the day of the week they will be sexually active. When the physician starts talking to patients about the reality of their sex lives, they realize, "It's not such a big deal." He stressed that this education is crucial—as important as the identification of ED and initial education, is the follow-up in the physician's office.

Dr. Carson brought up a subject that had been addressed by Dr. McCullough in a recent AUA 2001 presentation, namely that patients shouldn't expect to have optimum results with the first pill that they take. That, Dr. Carson said, is a piece of the patient coaching that is required of the physician and will be present with all the subsequent medications. The points to stress to the patient are these: take the drugs without a heavy meal, wait a reasonable period of time, and realize that the drug may be effective for longer than 6 hours. Patients may have the expectation that they will take the pill and see immediate results, as with injection therapy. This expectation should be addressed. Many patients may not need an hour, responding well before an hour is out. Stating that an hour is a conservative estimate is another part of the coaching. On the other hand, some patients, particularly men over 65, may need more than an hour.

Another point to stress, Dr. Carson noted, is that it may take six to eight doses of sildenafil before the patient has an optimum response. That is something that many patients don't accept easily. The physician must encourage them that they will need to use all six pills of the sample pack, or even more perhaps, before they have a good response. Multiple doses make sense, Carson continued, because for somebody who hasn't had sex with their partner for 2 or 3 years, obviously there are more issues involved than just the man's ability to maintain an erection. It is going to take more than one pill to solve all the other problems that go along with the lack of sex for two years.

With respect to patients' concerns about side effects and safety, Dr. McCullough offered this experience, stressing that he was discussing off-label use. When he senses patient or partner has anxiety about safety or side effects with sildenafil, he will give the patient his first pill in the office, saying, "Here take the pill." The patient will of course say, "Well, I'm not going to have sex right now." "Precisely! You'll see what the side effects are with the first pill outside of the bedroom." The next step is for the patient to take the second pill with masturbation. So, by the time the patient is ready for his third pill, he's gotten use to taking the medication. If his partner is concerned about him taking the medication, he can tell his partner "Don't worry about this, the doctor gave me a pill in the office." The patient has already taken two pills, is comfortable with the medication, and the partner will pick up on his comfort level. To use a metaphor, it's like taking a car, which has been in the shop for the past 18 months, on a test drive before trying it on the "open road."

Dr. Steers brought up the issue of treating the diabetic patient. Smooth muscle, he noted, regardless of its origin (penile, vascular, gastric, or bowel) will not relax substantially under high glucose levels. There are tremendous pharmacologic, electrical, and mechanical impairments in a high-glucose environment. Dr. Carson observed that data exists that shows very clearly that the number of diabetic complications is correlated negatively with the efficacy of sildenafil. He also felt that sildenafil works best in those patients that have better control of their glucose levels. Steers agreed, noting he uses the probability of sildenafil being more effective in a euglycemic environment as a "stick" to motivate the patient to get his blood sugar under better control.